Spring 1950

Investigation of The Iodination of Some of The Ortho Substituted Phenols

Horace S. Higgens
Fort Hays Kansas State College

INVESTIGATION OF THE IODINATION OF SOME OF THE ORTHO SUBSTITUTED PHENOLS

being

A thesis presented to the Graduate Faculty
of the Fort Hays Kansas State College in
partial fulfillment of the requirements for
the Degree of Master of Science

by

Horace S. Higgins, B. S.
Fort Hays Kansas State College

Date May 18, 1950 Approved Harold S. Choguill
Major Professor

Chairman Graduate Council

ACKNOWLEDGMENTS

The writer wishes to acknowledge his indebtedness to Dr. Harold S. Choguill, under whose direction this thesis was prepared, for his helpful suggestions. Acknowledgment is due to Dr. F. B. Streeter for his advice and willing cooperation at all times. Special acknowledgment is due to Mr. Arlin E. Mills for his exhaustive efforts in compiling a bibliography of "The Iodination of Organic Compounds" from Chemical Abstracts (1929-1948).

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INTRODUCTION

The use of phenol as a disinfectant dates back to Joseph Lister, who introduced it into medicine and surgery in 1865. Phenol itself plays a minor role today as a disinfectant. It is caustic and irritating when applied to the skin, and its odor is offensive to some people. The phenolic group of compounds is extensively used today as disinfectants. Such compounds are relatively cheap and, for the most part, very active bactericides. They differ from some other germicides in that they are only slightly soluble in water(23).

When phenol coefficients are calculated on the basis of iodine itself, values ranging from 155 to 235 are obtained. Iodine trichloride (ICl_3) and iodoform are used as germicides. Several aromatic iodine compounds exhibit bactericidal properties. Small concentrations of 2,3,5-triiodobenzoic acid, 3,5-diiodo-2-hydroxybenzoic acid; 2,4,6-triiodophenol, and several other such compounds are quite inhibitory to growth(24).

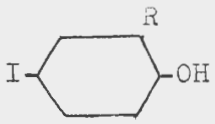
It has been shown by Klarmann and his associates (1929, 1934), that the germicidal activity of phenol, cresols, and resorcinol is increased by the substitution of halogens into their molecules(25).

Halogen substitution intensifies the microbial potency of phenol derivatives, the presence of halogen in the para-position to the hydroxyl group being more effective in this respect than in the ortho-position. The effect of halogen substitution, in general, increases with increasing atomic weight of the halogen. However, the effect of iodine has been little studied. Increasing the number of hydroxyl groups attached to an aromatic nucleus decreases the germicidal activity, a decrease that cannot effectively be compensated for by halogen when more than two hydroxyl groups are present(26).

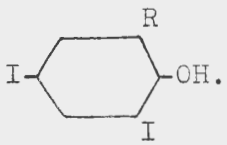
Since the halogen atom increases the bactericidal activity of phenol, it is interesting to note the cumulative effect when two or more halogen groups are present. For example, o-chlorophenol has a phenol coefficient of 3.6. The same molecule with another chlorine atom attached to the ring of the phenol, 2,4-dichlorophenol, has a phenol coefficient of 13.3. When three atoms of chlorine are attached to phenol, 2,4,6-trichlorophenol, the phenol coefficient is 22.6. From this it appears that the effect of a halogen atom on the phenol coefficient depends on the number of other halogen atoms already substituted in the phenol(27).

The purpose of this investigation was to see if

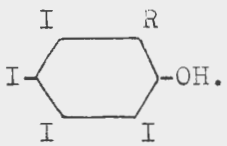
some of the iodinated o-phenols could be prepared. The compounds would probably be of the type



if the substitution of a single iodine occurs. Substitution of two atoms of iodine would probably produce a compound of the type



Substitution of four atoms of iodine would probably be of the type



In this investigation the ortho substituted phenols used were o-cresol, o-chlorophenol, o-hydroxybenzaldehyde, salicylic acid, methyl salicylate, ethyl salicylate, 8-hydroxyquinoline, o-cyclohexyl phenol, o-octyl phenol, and o-nitrophenol. One member of the group, o-benzylphenol, was not obtainable at the time of the investigation.

The bactericidal, germicidal and fungicidal activities

of the iodinated ortho substituted phenols were not determined in this investigation due to lack of time. In addition, the investigator has not had experience in bacteriology or mycology and feels that such an investigation should be carried out by someone with experience in that field.

THEORY AND METHOD OF INVESTIGATION

Iodination may be defined as the process whereby one or more iodine atoms are introduced into an organic compound. Iodination may involve reaction of (1)addition; (2)substitution of hydrogen; (3)replacement of groups[10].

The methods employed in iodination differ somewhat from those for chlorination or bromination. The relatively low chemical affinity, low heat of reaction, that distinguishes iodine from other halogens makes permanent, direct union of carbon to iodine by the replacement of hydrogen possible only in exceptional cases. Such iodinations are reversible in character, as for instance, the iodination of acetic acid:

$$CH_3.COOH + 2I \rightleftharpoons CH_2ICOOH + HI$$

and are governed largely by the condition employed. The hydrogen iodide tends to effect deiodination of the halogenated compounds and is sometimes thus employed. The successful conduction of iodination requires the removal of the hydrogen iodide as soon as it is formed by such means as oxidation, or absorption in alkali. When nitric acid is employed as the oxidant, practically all of the iodine enters the organic compound[11].

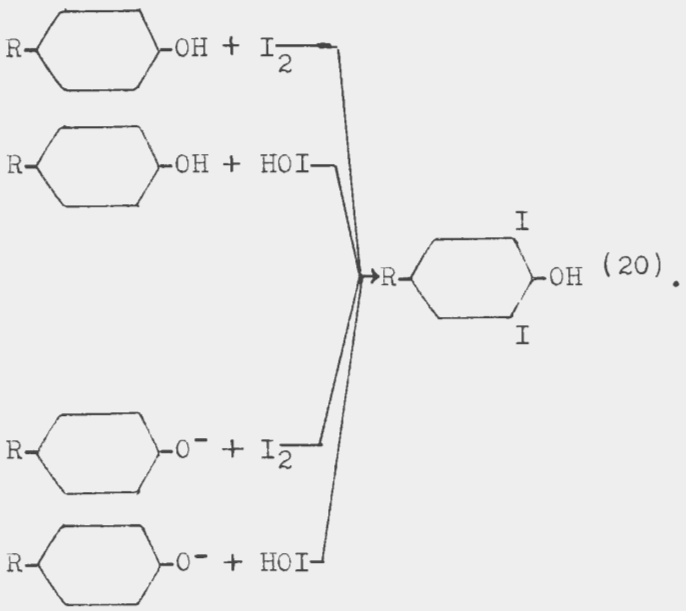
Catalysts are only infrequently employed in iodination, phosphorous being the principal accelerator[12].

Direct substitution of iodine into the benzene nucleus is feasible only in the presence of an oxidizing agent. The hydrogen iodide formed simultaneously with the iodo compound is loosely bound; and conditions must therefore be provided to avoid reversibility[13].

Phenols may be iodinated by treatment with iodine in the presence of strong ammonia. 2,4,6-Triiodophenol is prepared quantitatively by treatment of phenol in concentrated aqueous ammonia with iodine until the color of iodine persists. Phenolic compounds, in general are susceptible to the foregoing method[14].

The mechanism of the iodination of phenol is very confusing. The early investigations of Lofman(1919) gave the conclusion that the active iodination agent was hypoiodous acid and free iodine apparently had no direct iodinating effect; he concluded further that the positive iodine ion was the halogenating agent[17]. Later Soper and Smith(1924) showed that the iodination of phenol is not caused by the positive iodine ion, but that the main reactions are those between the hypoiodous acid and the ionized and unionized phenol[18].

In the iodination of tyrosine, Choh Hao Li (1941) suggest that iodination may involve four paths, namely; (1)iodine and phenol, (2)iodine and phenolate, (3)hypoiodous acid and phenol, and (4)hypoiodous acid and phenolate. The importance of each path is determined by the pH and iodide ion concentrations. Thus path (4) is the main path for the formation of iodinated phenol in slightly alkaline solution[19]. These four are represented by the following equations



(20).

Choh Hao Li also makes the statement that in highly

alkaline solution the iodination reaction is instantaneous if the concentration of the hypoiodite ion is maintained. He also assumes that as soon as one iodine atom enters the ring, the other atom of iodine follows immediately[21].

Iodine carriers in a strict sense are not known as carriers, as bromine and chlorine are known. Iodine does not substitute into an aromatic nucleus with the use of iron or aluminum chloride as do bromine and chlorine.

The use of iodine mono- or trichlorides might possibly be considered carriers. Iodine monochloride, ICl, apparently first chlorinates the organic compounds and then changes them subsequently to iodine compounds. These reactions proceed one after the other according to the general equation,

$$C_xH_y + ICl \longrightarrow C_xH_{y-1}I + HCl.$$

However, the reaction succeeds only in cases in which the substitution of hydrogen atoms takes place readily. Such is the case with phenol[31]. Block and Powell have succeeded in iodinating tyrosine by the use of iodine monochloride, ICl[1].

Since iodination generally takes place most readily in the presence of substances which combine with hydrogen iodide produced. From this consideration liquid ammonia

would appear to be suitable medium in which to carry out iodination since any hydrogen iodide produced would at once react with the ammonia to produce ammonium iodide[30]. Iodination of halogenated phenols has been effected by means of a solution of iodine in potassium iodide in the presence of concentrated ammonium hydroxide[29]. Choguill used the method of solution of iodine in potassium iodide in the presence of concentrated ammonium hydroxide in the iodination of hydroxy derivatives of diphenyl ether[5]. In the method of using a solution of iodine in potassium iodide in the presence of ammonium hydroxide, the actual iodinating agent appears to be the active nitrogen triiodide from iodine and ammonia[6].

In this investigation of the iodination of the o-substituted phenols, the method using iodine in potassium iodide solution in the presence of ammonium hydroxide solution was chosen. This method is very convenient and all the chemicals and apparatus necessary for such a method of iodination were available. It is assumed in this investigation that the active nitrogen triiodide is the iodinating agent.

Certain rules have been formulated for predicting position of the iodine atoms entering the benzene ring. If a second substituent, Y, is to be introduced into a

benzene derivative C_6H_5A, the position taken by Y depends upon the electronic character of the group A already present on the ring. Whether the disubstituted products are ortho and para or meta is closely associated with the speed of the substitution. Cases of rapid substitution lead to the formation of ortho and para compounds. Substitution in certain other benzene derivatives is extremely slow and meta substitution products are formed. If a compound C_6H_5A is to undergo a second substitution to produce C_6H_4XY, the readiness with which such a reaction will proceed will depend upon whether the resonance forms of C_6H_5X are such as to increase or decrease the electron density of the ring. The increase in electron density results in an "activation" of the ri g[2].

Orienting powers of different groups are listed below.

Class I. Ortho-para orienting groups (Electron donor.)

A. Very strong: $-N(CH_3)_2$; $-NH_2$; $-OH$

B. Intermediate: $-NHCOCH_3$; $-OCOCH_3$; $-OCH_3$

C. Comparatively weak: $-Cl$; $-Br$; $-I$; $-CH_3$

Class II. Meta orienting groups (Electron acceptors).

$NO_2 > SO_3H > CN > COOH > CHO$

Any group in division A of Class I has greater directing power than any group in division B, which, in turn, exceeds

any group in division C. The NO_2 group of Class II, which produces a large electron deficit on the ring, will be more definitely meta-directing than one such as COOH which causes a smaller electron deficit. The speed of substitution is greater when a COOH group is present than when a nitro group is present, but the proportion of meta disubstitution is less[3].

The rules of substitution are:

1. The group already present on the benzene ring determine the position taken by the next entering group.

2. Class I groups direct a new group to the ortho or para position, and the rate of substitution is faster than it is in benzene.

3. Class II groups direct a new group to the meta position, and the rate of substitution is slower than it is in benzene.

4. Class I groups always take precedence over Class II groups in benzene derivatives which contain a representative of each class[4].

The course of the reaction during the iodination of the o-substituted phenols was followed potentiometrically. The usual method of measuring two potentials without the passage of appreciable current is by means of a potentiometer,

a diagram of which is shown in Fig. I. AD is a uniform slide wire, R is a variable resistance, B a battery, SC a standard Weston cell, G a galvanometer, and K a tapping key which completes the circuit only momentarily(34).

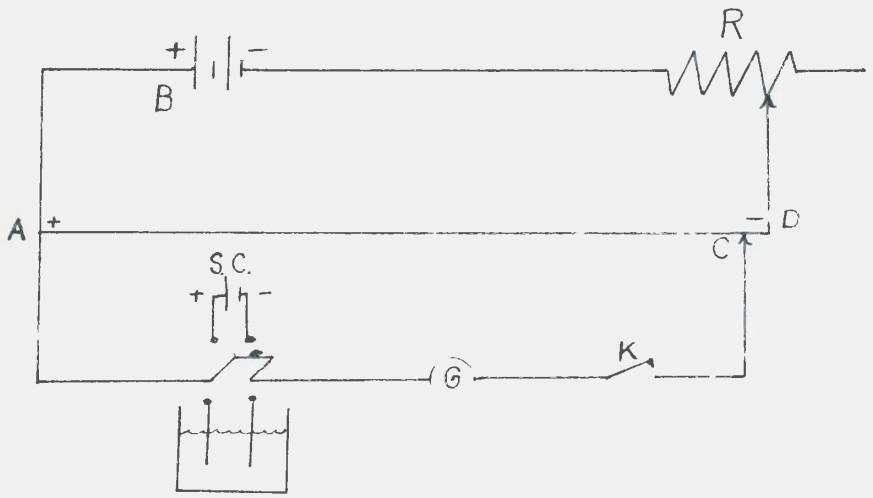


Figure 1. Diagram of Potentiometric Circuit

The potential drop along the slide wire from A to D is accurately calibrated by setting AC to the potential of the Weston cell and adjusting the resistance R until the galvanometer shows no deflection on closing the key. Thereafter, the two electrodes to be measured are inserted in place of the Weston cell, and the distance AC adjusted until the galvanometer again shows no deflection on closing the key. The potential drop from A to C then is the difference of the potentials of the two electrodes.

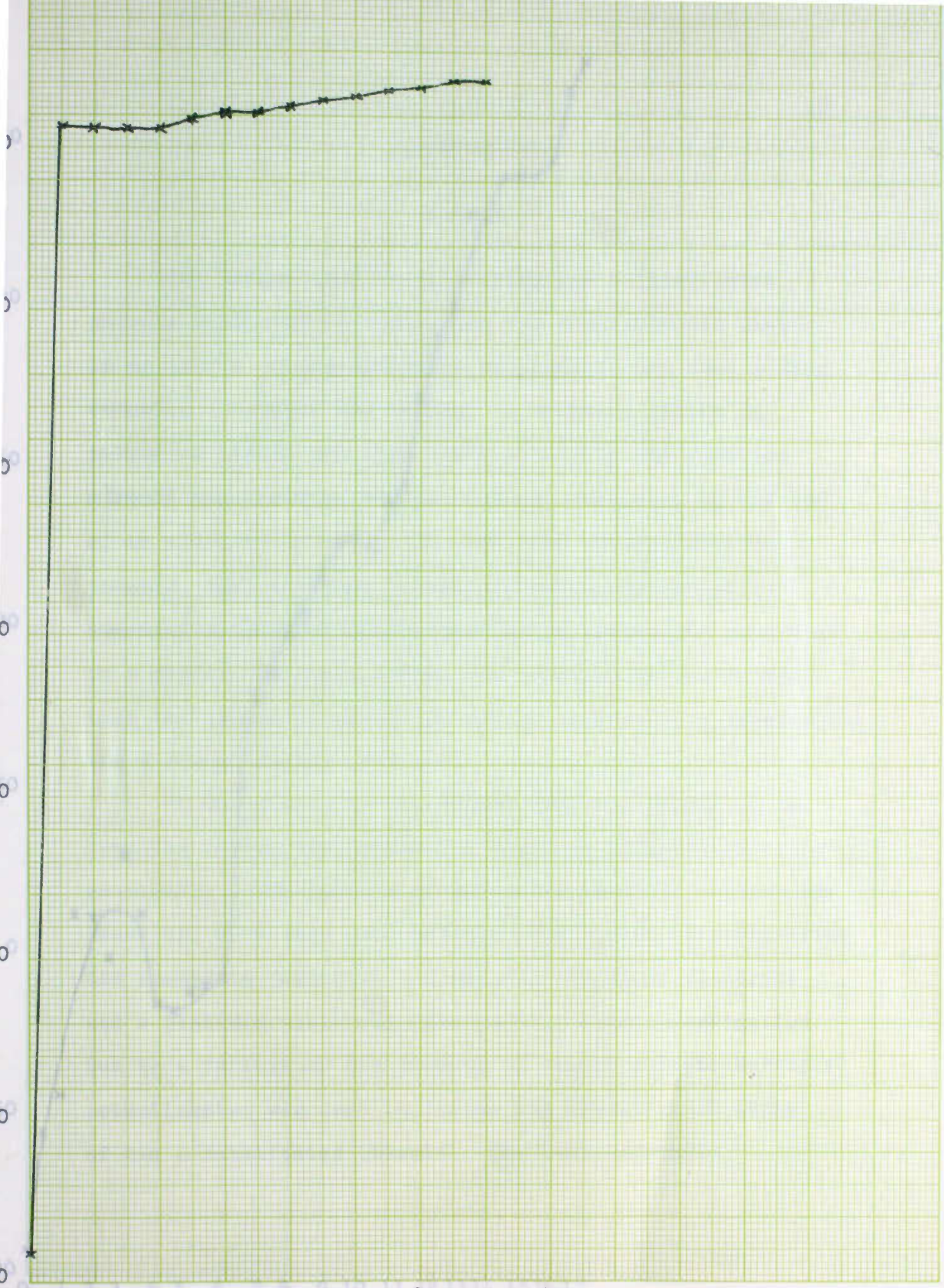
In recent years the measurement of potential has been simplified by the introduction of vacuum tube voltmeters. One of these instruments will draw so little current from the cell under measurement that it may be connected directly to the two electrodes. The Beckman pH meter is that type of an instrument; it is so calibrated that the pH of the solution may be read directly or voltage in millivolts may be read.

In following the course of the reaction, a calomel half-cell was used as a reference electrode of constant potential. Other reference electrodes are discussed by Willard, Merrit, and Dean[35]. The other electrode used was a platinum electrode. The potential of the platinum electrode, used in conjunction with the calomel half cell, is a function of the ion activity of the solution in which it is immersed. It is possible that by measurement of the variation electromotive force in millivolts of the solution of o-substituted phenols being iodinated, the mechanism of iodination may be clarified to some extent.

Gill(1950) in the iodination of p-cresol carried out the iodination in different concentrations of ammonium hydroxide to see if iodination would proceed the same under conditions of different concentrations of ammonium

hydroxide, or whether iodination was favored by any particular concentration of ammonium hydroxide. He used ammonium hydroxide that contained 7.1% ammonia in the iodination of the p-alkylphenols(7).

Gill prepared tri-iodophenol by using the method of iodine in potassium iodide solution in presence of ammonium hydroxide and the course of the reaction was followed with a Beckman pH meter. Fig. 3 shows the potential curve obtained(8). Gill also followed the reaction between a 7.1% solution of ammonia and iodine in potassium iodide solution. The potential curve, Fig. 2, that was produced shows the effect when iodine does not react with phenol(9).



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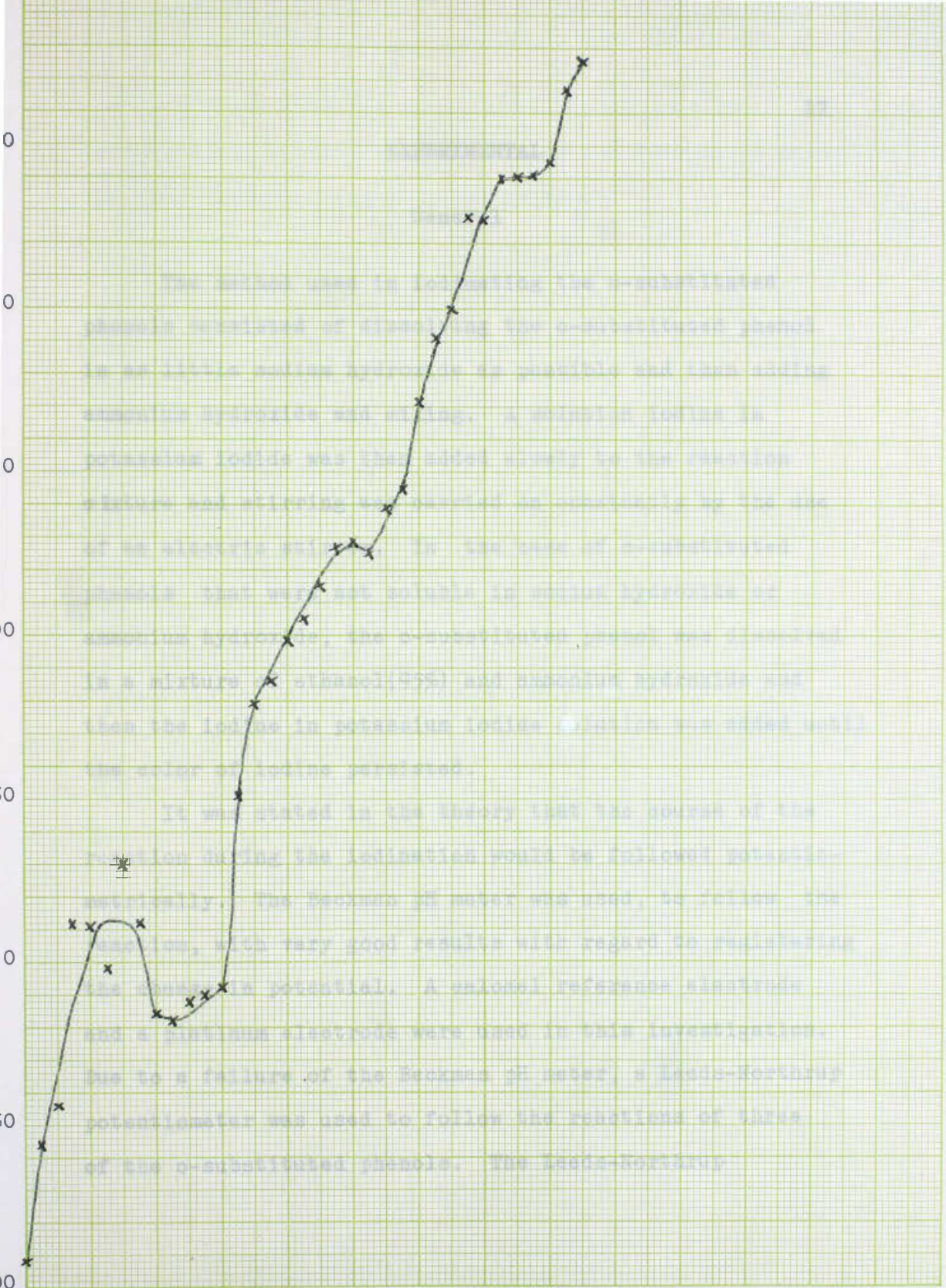

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EXPERIMENTAL

General

The method used in iodinating the o-substituted phenols consisted of dissolving the o-substituted phenol in as little sodium hydroxide as possible and then adding ammonium hydroxide and mixing. A solution iodine in potassium iodide was then added slowly to the reaction mixture and stirring was carried on constantly by the use of an electric stirrer. In the case of o-substituted phenols that were not soluble in sodium hydroxide or ammonium hydroxide, the o-substituted phenol was dissolved in a mixture of ethanol(95%) and ammonium hydroxide and then the iodine in potassium iodide solution was added until the color of iodine persisted.

It was stated in the theory that the course of the reaction during the iodination would be followed potentiometrically. The Beckman pH meter was used, to follow the reaction, with very good results with regard to registering the change in potential. A calomel reference electrode and a platinum electrode were used in this investigation. Due to a failure of the Beckman pH meter, a Leeds-Northrup potentiometer was used to follow the reactions of three of the o-substituted phenols. The Leeds-Northrup

potentiometer was not as sensitive as the Beckman pH meter but good results were obtained using it.

Analysis

The iodine compounds obtained were analyzed for iodine by means of the Parr Bomb[22].

Two tenths gram of the compound to be analyzed was mixed with 15 grams of sodium peroxide and 1 gram of cane sugar in a Parr Bomb. The bomb was then ignited; the contents were dissolved in water and boiled to remove hydrogen peroxide. Iodates were reduced to iodides by means of an excess of hydrazine sulfate solution. The iodine was then determined as iodide by the Volhard method[15].

Saponification equivalents of the two esters were determined by the Diethylene Glycol method[28].

Two tenths gram of the ester to be analyzed was placed in a small glass-stoppered Erlenmeyer flask and exactly 10 ml. of 0.9978N. potassium hydroxide in diethylene glycol added. The reaction mixture was then heated to 130°C, with shaking, on an oil bath. The reaction mixture cooled and titrated with 0.5065N hydrochloric acid.

Preparation of Diiodo-o-cresol from o-Cresol

One gram of o-cresol was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 63°C, Willgerodt reported 69.5°C. The equation for the reaction is

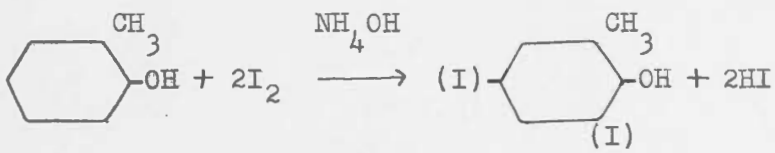
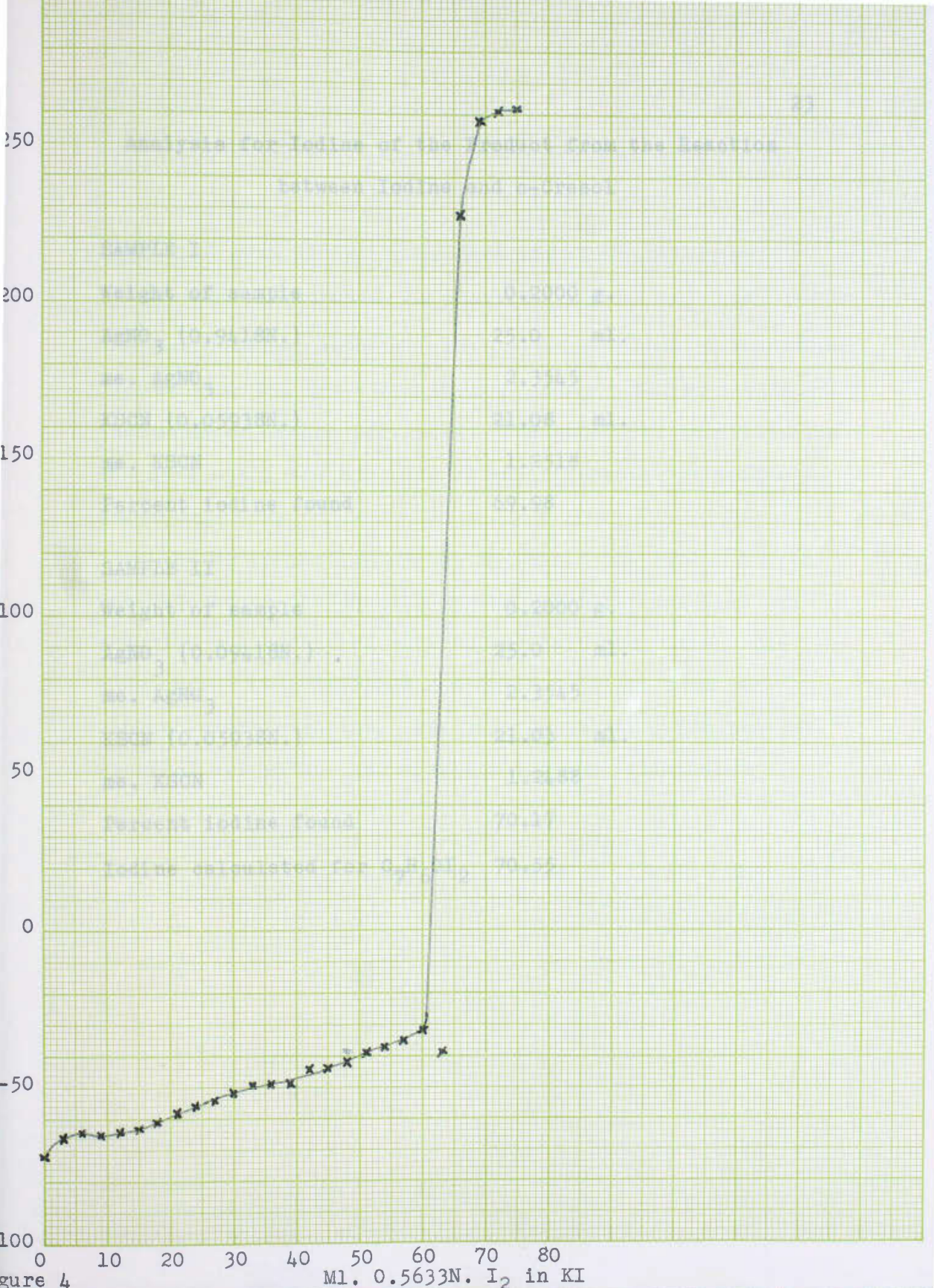


TABLE I

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-CRESOL IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	- 72	
3	- 66	
6	- 64	
9	- 65	
12	- 64	
15	- 63	
18	- 61	
21	- 58	
24	- 56	
27	- 54	
30	- 52	
33	- 49	
36	- 49	
39	- 49	
42	- 44	
45	- 44	
48	- 42	
51	- 39	
54	- 37	
57	- 35	
60	- 32	
63	- 39	
66	228	
69	258	I_2 color persisted
72	261	
75	262	


250
200
150
100
50
0
-50
100
0
10
20
30
40
50
60
70
80
Ml. 0.5633N. I_2 in KI

gure 4

Analysis for Iodine of the Product from the Reaction between Iodine and o-Cresol

SAMPLE I

Weight of sample	0.2000	g.
$AgNO_3$ (0.9418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	21.08	ml.
me. KSCN	1.2518	
Percent iodine found	69.98	

SAMPLE II

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	21.03	ml.
me. KSCN	1.2488	
Percent iodine found	70.17	
Iodine calculated for $C_7H_6OI_2$	70.55	

Preparation of Diiodo-o-chlorophenol from o-Chlorophenol

One gram of o-chlorophenol was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 99°C. The equation for the reaction is

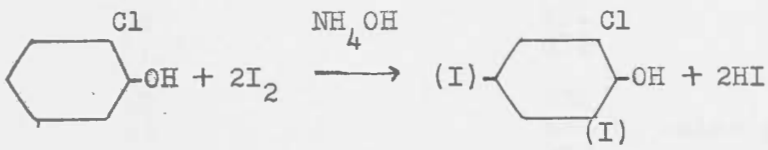
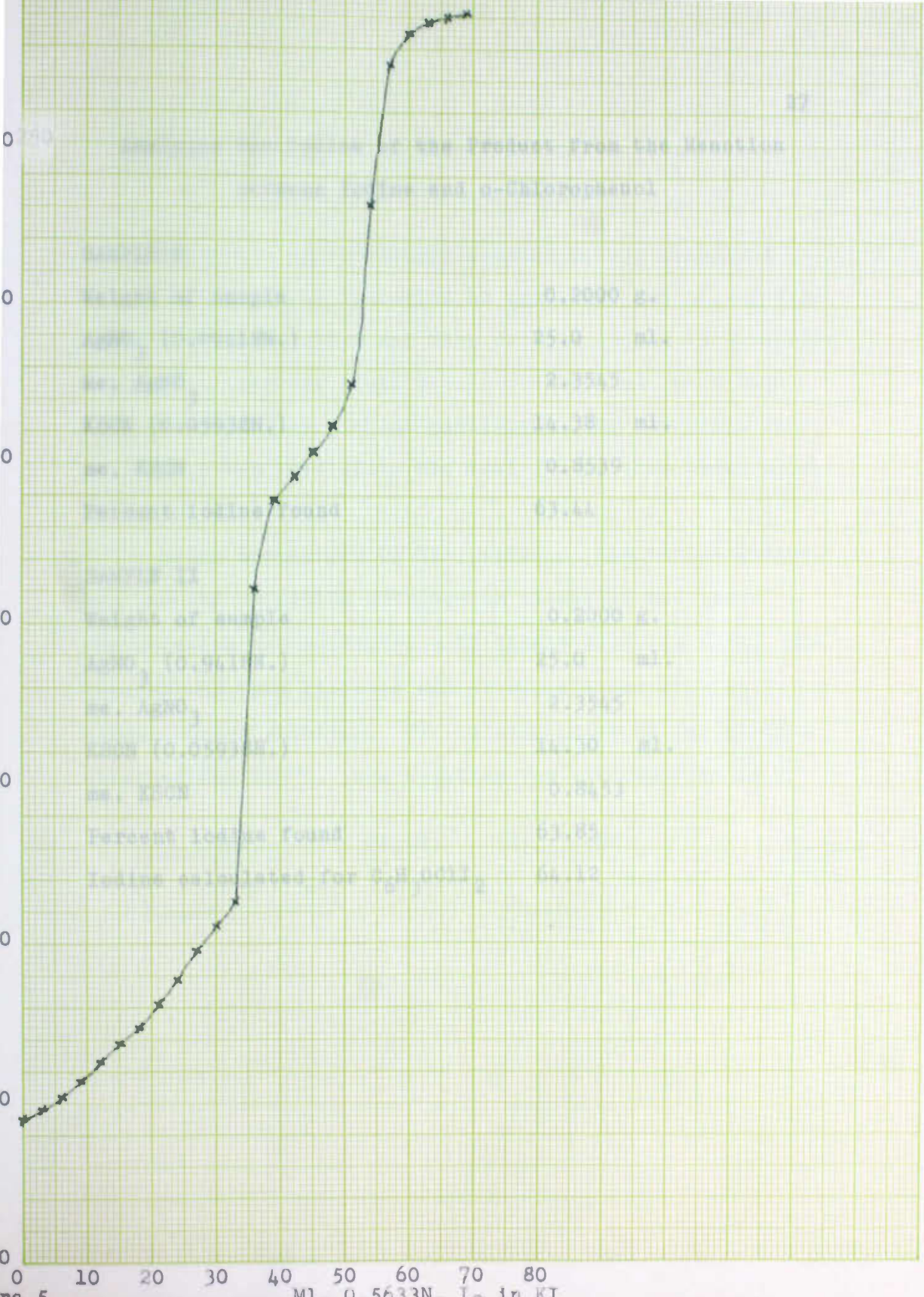


TABLE II

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-CHLOROPHENOL IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	- 55	
3	- 52	
6	- 48	
9	- 43	
12	- 37	
15	- 31	
18	- 26	
21	- 19	
24	- 11	
27	- 2	
30	6	
33	13	
36	111	
39	138	
42	146	
45	154	
48	162	
51	175	
54	231	
57	275	
60	284	
63	288	I_2 color persisted
66	290	
69	291	



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Analysis for Iodine of the Product from the Reaction between Iodine and o-Chlorophenol

SAMPLE I

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	14.38	ml.
me. KSCN	0.8539	
Percent iodine found	63.44	

SAMPLE II

Weight of sample	0.2000	g.
$AgNO_3$ (0.9418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	14.30	ml.
me. KSCN	0.8453	
Percent iodine found	63.85	
Iodine calculated for $C_6H_3OClI_2$	64.12	

Preparation of Tetraiodo-o-hydroxybenzaldehyde from o-Hydroxybenzaldehyde

One gram of o-hydroxybenzaldehyde was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 153°C. The equation for the reaction is

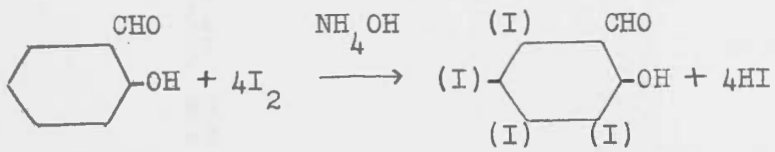
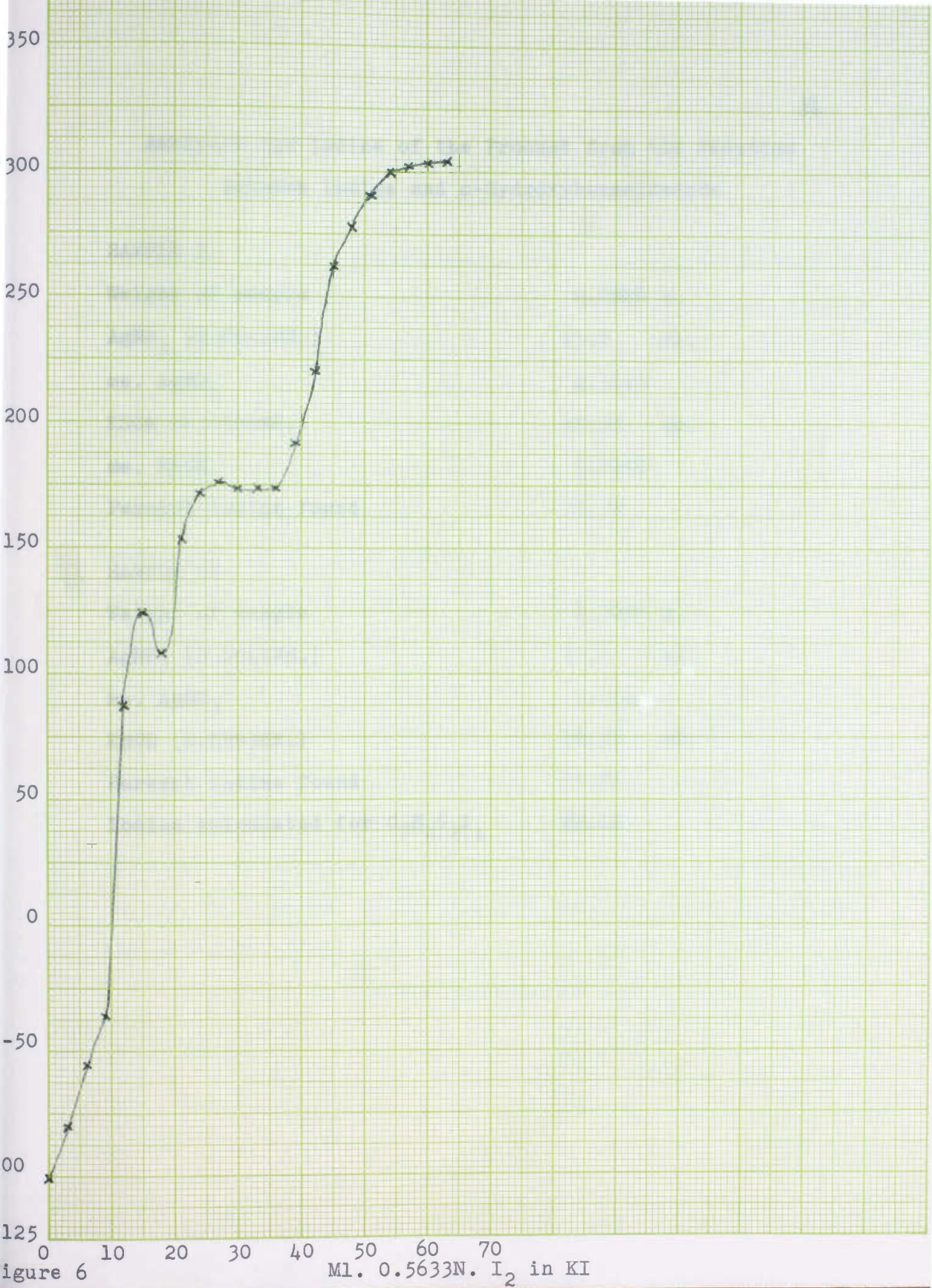


TABLE III

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-HYDROXYBENZALDEHYDE IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	-101	
3	- 80	
6	- 56	
9	- 36	
12	87	
15	124	
18	108	
21	153	
24	172	
27	176	
30	174	
33	174	
36	174	
39	192	
42	220	
45	262	
48	278	
51	290	
54	300	
57	302	I_2 color persisted
60	303	
63	304	


350
300
250
200
150
100
50
0
-50
00
125
0
10
20
30
40
50
60
70
Ml. 0.5633N. I_2 in KI

igure 6

Analysis for Iodine of the Product from the Reaction between Iodine and o-Hydroxybenzaldehyde

SAMPLE I

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	18.50	ml.
me. KSCN	1.0986	
Percent iodine found	79.70	

SAMPLE II

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	18.55	ml.
Percent iodine found	79.51	
Iodine calculated for $C_7H_2O_2I_4$	80.12	

Preparation of 3,4,5,6-Tetraiodosalicylic Acid from Salicylic Acid

One gram of salicylic acid was dissolved in as little sodium hydroxide as possible 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After the addition of iodine, the excess iodine was reduced to iodide with sodium bisulfite and then acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 155°-157°C.

This product is different from 3,5-diiodosalicylic acid obtained from the hydrolysis of 3,5-diiodomethyl salicylate and 3,5-diiodoethyl salicylate. It is assumed that the positioning of the four iodine atoms in tetraiodosalicylate acid are in the 3,4,5,6 positions with respect to the carboxyl group.

The equation for the reaction is

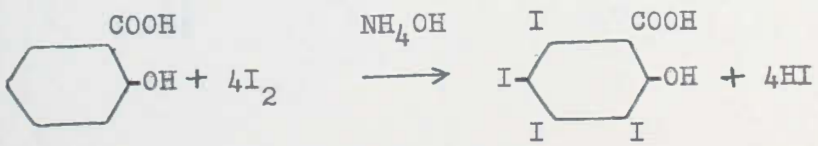
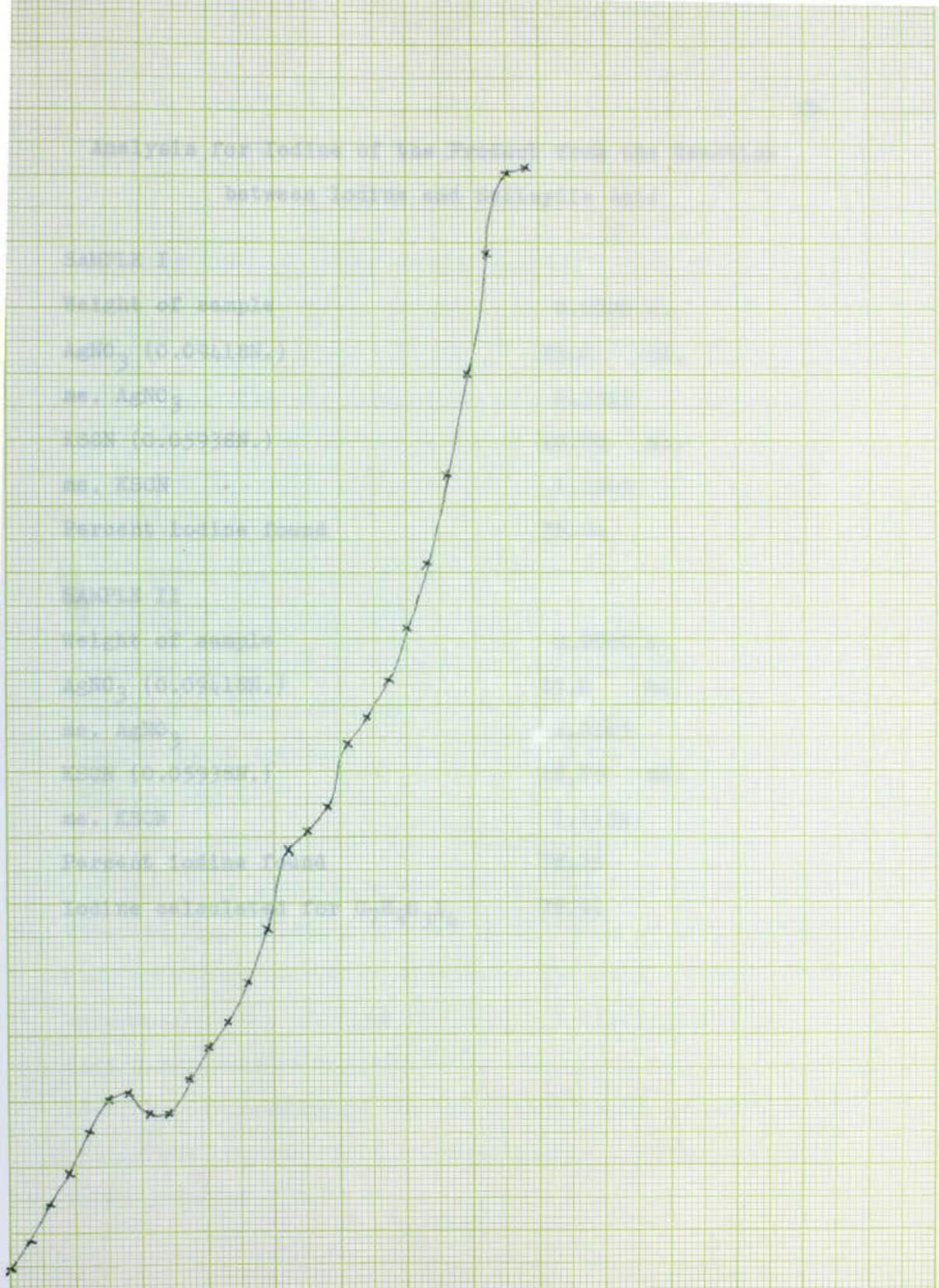


TABLE IV

POTENTIAL DATA FOR THE REACTION OF IODINE WITH SALICYLIC ACID IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	-138	
3	-128	
6	-114	
9	- 98	
12	- 87	
15	- 74	
18	- 72	
21	- 80	
24	- 80	
27	- 67	
30	- 55	
33	- 45	
36	- 30	
39	- 10	
42	20	
45	27	
48	37	
51	60	
54	70	
57	84	
60	104	
63	128	
66	162	
69	200	
72	245	I_2 color persisted
75	276	
78	277	



ure 7

Analysis for Iodine of the Product from the Reaction between Iodine and Salicylic Acid

SAMPLE I		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	18.70	ml.
me. KSCN	1.1105	
Percent iodine found	78.94	
SAMPLE II		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	18.75	ml.
me. KSCN	1.1134	
Percent iodine found	78.76	
Iodine calculated for $C_7H_2O_3I_4$	78.91	

Preparation of 3,5-Diiodomethyl Salicylate from Methyl Salicylate

One gram of methyl salicylate was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5502N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 108°-109°C.

The melting point of 3,5-diiodomethyl salicylate obtained from literature was 110°C.(16). The acid product obtained from diiodomethyl salicylate when it was reacted with potassium hydroxide decomposed at 228°C. From information obtained in literature 3,5-diiodosalicylic acid decomposes at ± 230°C.(16). From this one could assume that the positioning of the two iodine atoms in diiodomethyl salicylate are in the 3,5 positions with respect to the ester grouping.

The equation for the reaction is

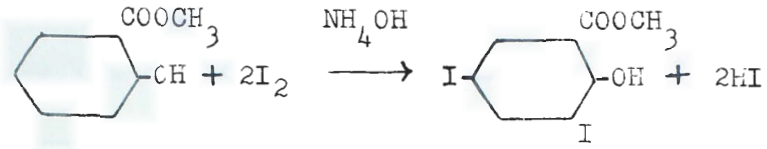
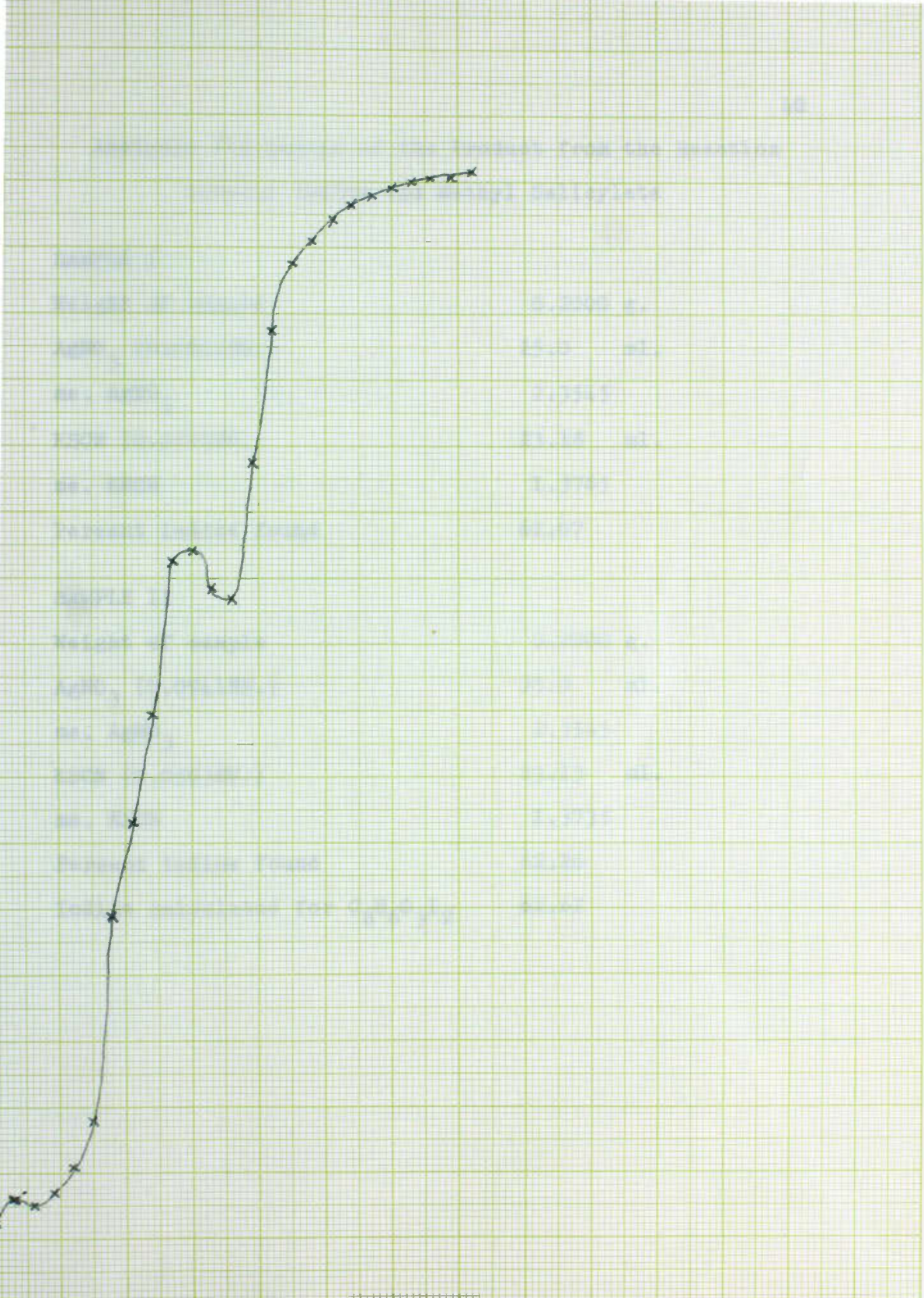


TABLE V

POTENTIAL DATA FOR THE REACTION OF IODINE WITH METHYL SALICYLATE IN 7.1% AMMONIA SOLUTION

Ml. 0.5502N Iodine	Potential in Millivolts	
0	- 25	
3	- 18	
6	- 20	
9	- 16	
12	- 8	
15	6	
18	68	
21	96	
24	139	
27	175	
30	178	
33	167	
36	164	
39	205	
42	245	
45	265	
48	272	
51	278	
54	283	
57	286	
60	288	I_2 color persisted
63	290	
66	291	
69	291	
72	293	


10
20
30
40
50
60
70
80
Ml. 0.5202N. I_2 in KI

Analysis for Iodine of the Product from the Reaction between Iodine and Methyl Salicylate

SAMPLE I		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	23.18	ml.
me. KSCN	1.3765	
Percent iodine found	62.07	
SAMPLE II		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	23.13	ml.
me. KSCN	1.3735	
Percent iodine found	62.26	
Iodine calculated for $C_8H_6O_3I_2$	62.62	

Saponification Equivalent for

3,5-Diiodomethyl Salicylate

Weight of Sample	0.2000	g.
Alkali (0.9978N.)	10.0	ml.
Acid (0.5065N.)	18.75	ml.
Saponification Equivalent found	406.5	
Saponification Equivalent calculated for $C_8H_6O_3I_2$	404	

Preparation of 3,5-Diiodoethyl Salicylate from Ethyl Salicylate

One gram of ethyl salicylate was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5502N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 104°-105°C.

The melting point of 3,5-diiodoethyl salicylate obtained from literature was 132°-133°C.[16]. The acid product from diiodoethyl salicylate when it was reacted with potassium hydroxide decomposed at 228°C. From information obtained in literature 3,5-diiodosalicylic acid decomposes at ± 230°C.[16]. From this one could assume that the positioning of the two iodine atoms in diiodoethyl salicylate are in the 3,5 positions with respect to the ester grouping.

The equation for the reaction is

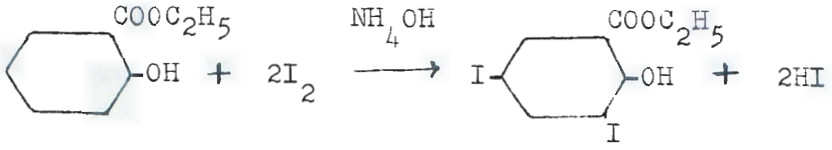
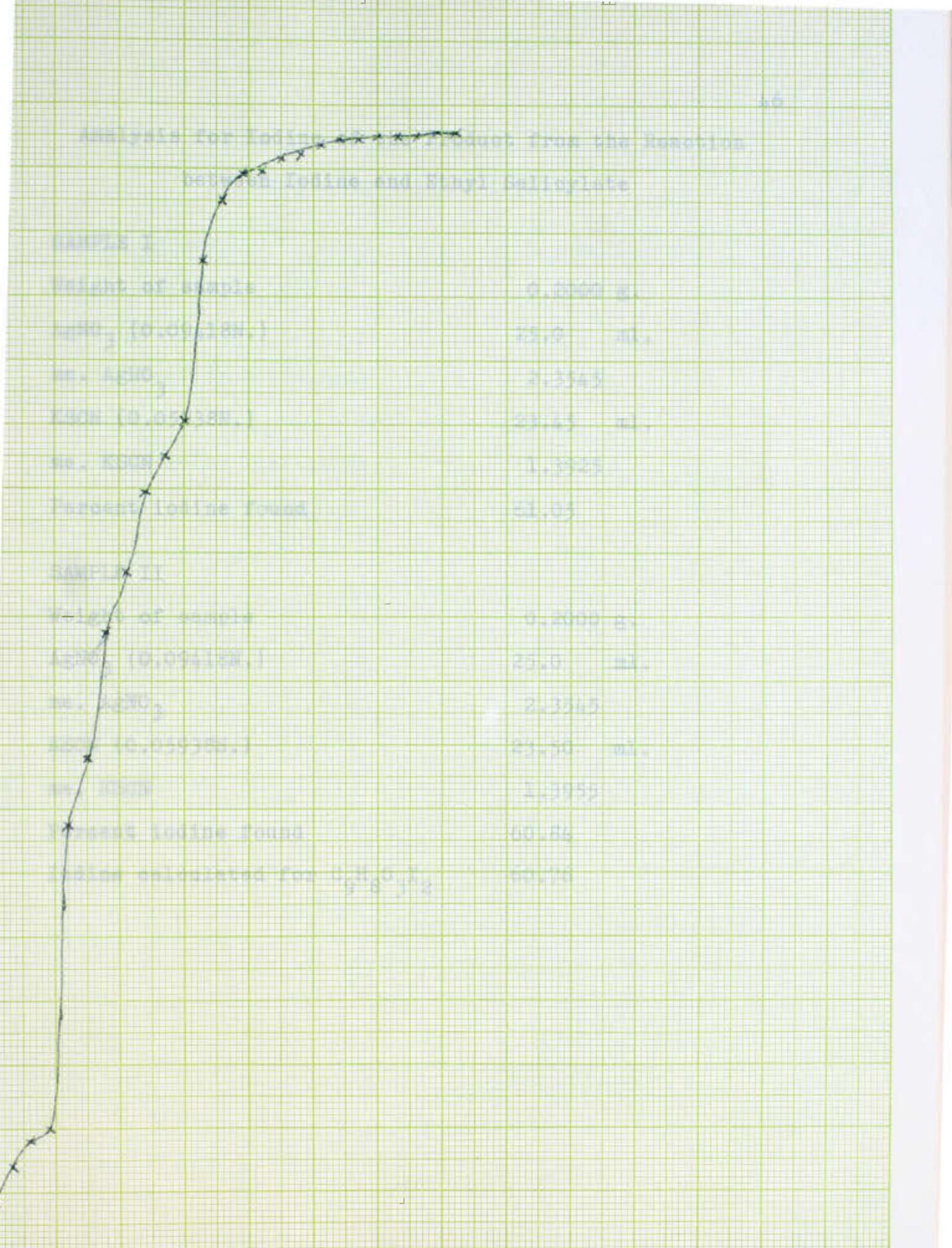


TABLE VI

POTENTIAL DATA FOR THE REACTION OF IODINE WITH ETHYL SALICYLATE IN 7.1% AMMONIA SOLUTION

Ml. 05502N Iodine	Potential in Millivolts	
0	- 33	
3	- 22	
6	- 14	
9	10	
12	85	
15	106	
18	145	
21	164	
24	189	
27	200	
30	211	
33	261	
36	280	
39	288	
42	289	
45	293	
48	294	
51	297	
54	299	
57	299	I_2 color persisted
60	300	
63	300	
66	300	
69	301	
72	301	


0
10
20
30
40
50
60
70
80
Ml. 0.5202N. I_2 in KI

Analysis for Iodine of the Product from the Reaction between Iodine and Ethyl Salicylate

SAMPLE I		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	23.45	ml.
me. KSCN	1.3925	
Percent iodine found	61.05	
SAMPLE II		
Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	23.50	ml.
me. KSCN	1.3955	
Percent iodine found	60.84	
Iodine calculated for $C_9H_8O_3I_2$	60.76	

Saponification Equivalent for

3,5-Diiodoethyl Salicylate

Weight of Sample	0.2000	g.
Alkali (0.9978N.)	10.0	ml.
Acid (0.5065N.)	18.55	ml.
Saponification Equivalent found	415	
Saponification Equivalent calculated for $C_9H_8O_3I_2$	418	

Preparation of Monoiodo and 5,7-Diiodo 8-Hydroxyquinoline from 8-Hydroxyquinoline

One gram of 8-hydroxyquinoline was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. The product was then filtered and recrystallized from an ethanol-water solution. The melting point of the product obtained was 150°-153°C. The insoluble product from the ethanol-water solution was recrystallized from 95% ethanol. The product obtained melted at 206°-207°C. The product had approximately the same melting point as a known sample of 5,7-diiodo-8-hydroxyquinoline[37]. When the product obtained and 5,7-diiodo-8-hydroxyquinoline were mixed, the melting point was not depressed. The above statements indicate that the position of the iodine atoms in the

diiodio derivatives are in the 5,7 positions with respect to the heterocyclic nitrogen atom.

The equations for the reactions are

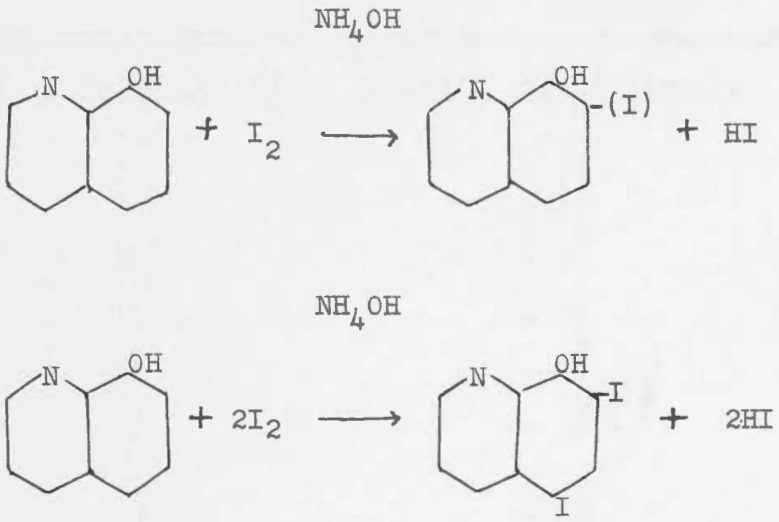
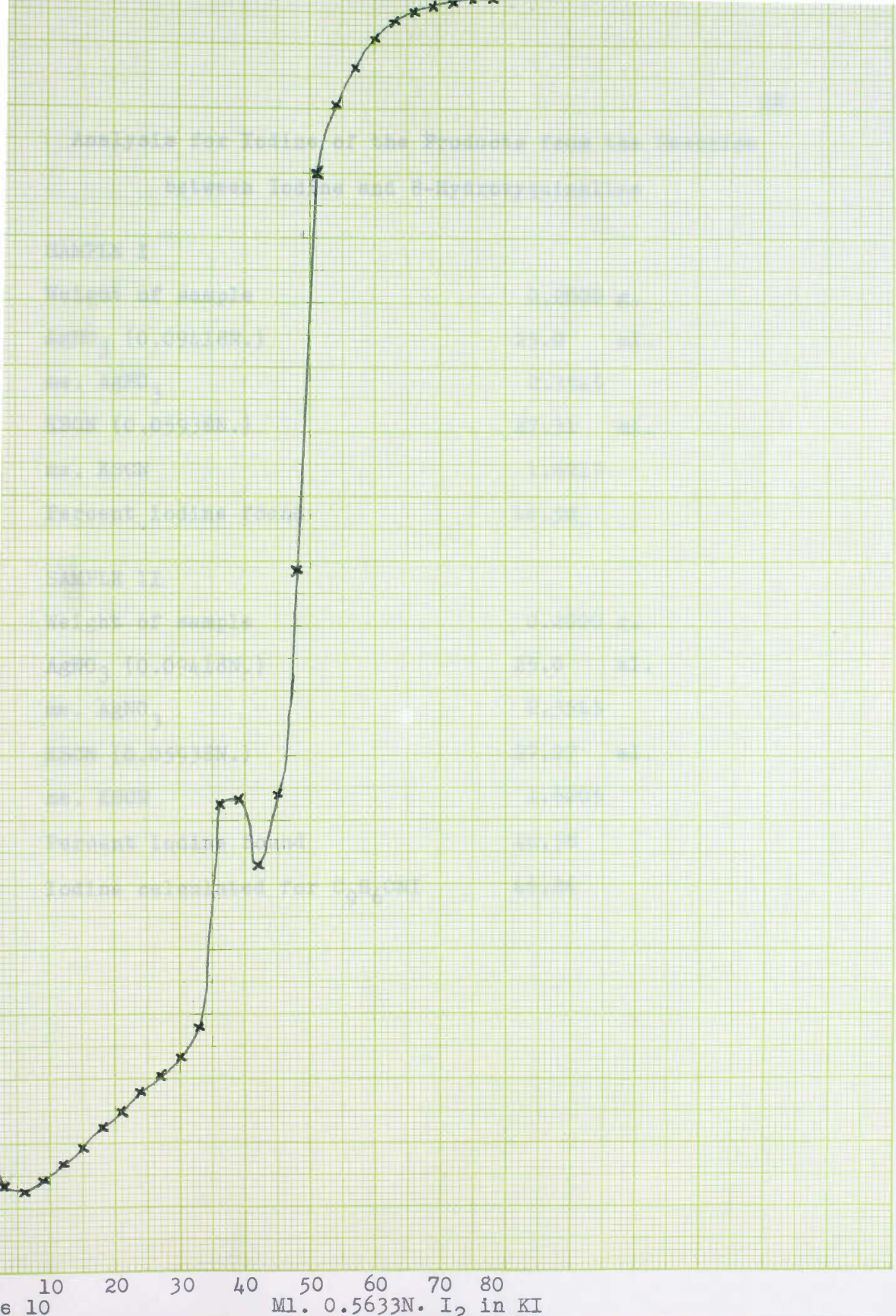


TABLE VII

POTENTIAL DATA FOR THE REACTION OF IODINE WITH 8-HYDROXYQUINOLINE IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	- 55	
3	- 73	
6	- 75	
9	- 71	
12	- 66	
15	- 61	
18	- 55	
21	- 50	
24	- 44	
27	- 39	
30	- 33	
33	- 24	
36	45	
39	47	
42	26	
45	48	
48	117	
51	240	
54	261	
57	273	
60	282	
63	287	I_2 color persisted
66	290	
69	292	
72	293	
75	294	
78	294	


10 20 30 40 50 60 70 80
e 10
Ml. 0.5633N. I_2 in KI

Analysis for Iodine of the Products from the Reaction between Iodine and 8-Hydroxyquinoline

SAMPLE I

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	27.31	ml.
me. KSCN	1.6217	
Percent iodine found	46.50	

SAMPLE II

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	27.27	ml.
me. KSCN	1.6205	
Percent iodine found	46.58	
Iodine calculated for C_9H_6ONI	46.86	

SAMPLE I

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05638N.)	22.05	ml.
me. KSCN	1.3399	
Percent iodine found	64.39	

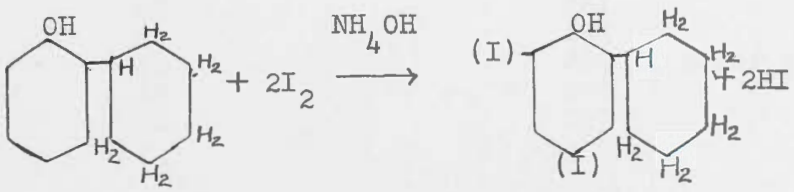
SAMPLE II

Weight of sample	0.2000	g.
$AgNO_3$ (0.09418N.)	25.0	ml.
me. $AgNO_3$	2.3545	
KSCN (0.05938N.)	22.10	ml.
me. KSCN	1.3439	
Percent iodine found	64.13	
Iodine calculated for $C_9H_5ONI_2$	63.97	

Reaction of Iodine with o-Cyclohexyl Phenol

One gram of o-cyclohexyl phenol was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5633N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. A heavy, dark purple tarry mass was obtained. Attempts were made to obtain a crystalline product but all failed. Qualitative examinations showed iodine to be present, but whether in solution or in combination, it could not be determined. The probable equation for the reaction is

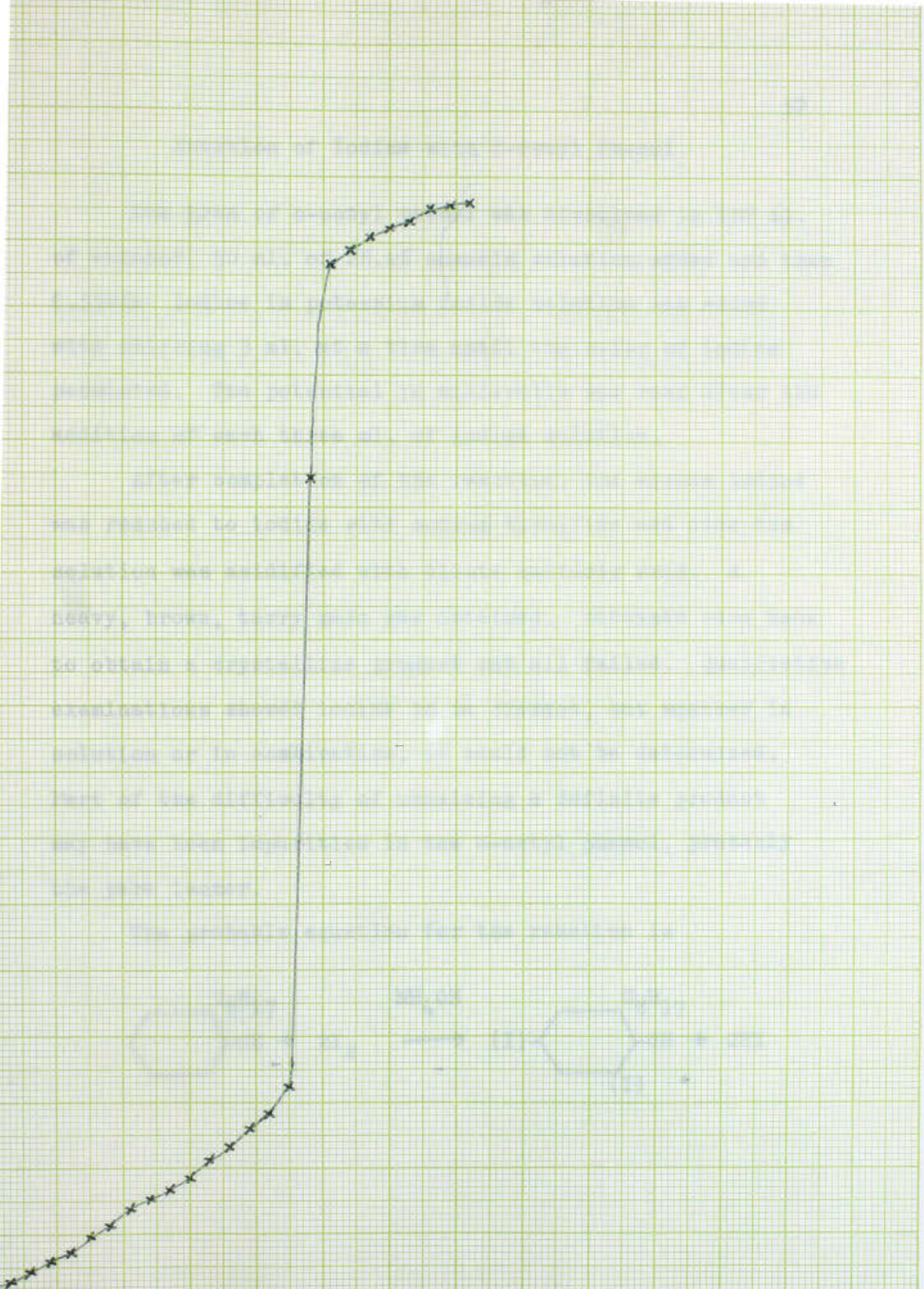


or a polymer.

TABLE VIII

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-CYCLOHEXYL PHENOL IN 7.1% AMMONIA SOLUTION

Ml. 0.5633N Iodine	Potential in Millivolts	
0	-119	
3	-118	
6	-114	
9	-111	
12	-107	
15	-101	
18	- 97	
21	- 91	
24	- 87	
27	- 83	
30	- 79	
33	- 72	
36	- 67	
39	- 60	
42	- 54	
45	- 44	
48	186	
51	267	
54	273	
57	277	
60	281	
63	283	
66	288	I_2 color persisted
69	289	
72	290	



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Reaction of Iodine with o-Octyl Phenol

One gram of o-octyl phenol was dissolved in 150 ml. of ethanol, 50 ml. of 28.4% ammonia solution added and then 0.5502N. iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. A heavy, brown, tarry mass was obtained. Attempts were made to obtain a crystalline product but all failed. Qualitative examinations showed iodine to be present, but whether in solution or in combination, it could not be determined. Part of the difficulty of obtaining a definite product may have been impurities in the o-octyl phenol, probably the para isomer.

The probable equation for the reaction is

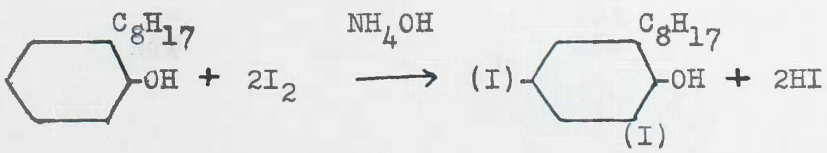
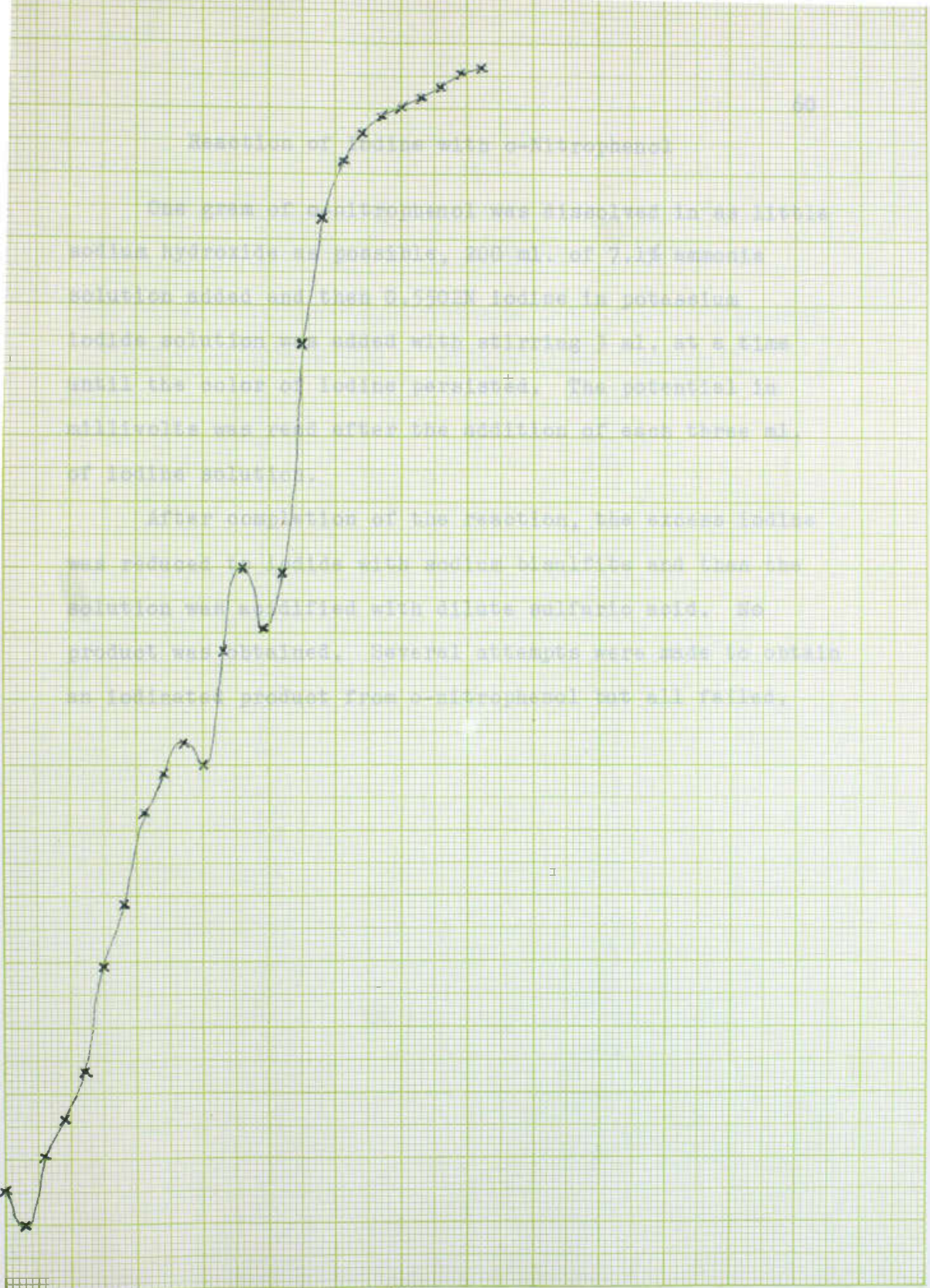


TABLE IX

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-OCTYL PHENOL IN 7.1% AMMONIA SOLUTION

Ml. 0.5502N Iodine	Potential in Millivolts	
0	- 52	
3	- 60	
6	- 44	
9	- 36	
12	- 25	
15	- 1	
18	13	
21	34	
24	43	
27	50	
30	45	
33	71	
36	90	
39	76	
42	89	
45	141	
48	170	
51	183	
54	189	
57	193	
60	195	
63	197	I_2 color persisted
66	200	
69	203	
72	204	



re 12

Reaction of Iodine with o-Nitrophenol

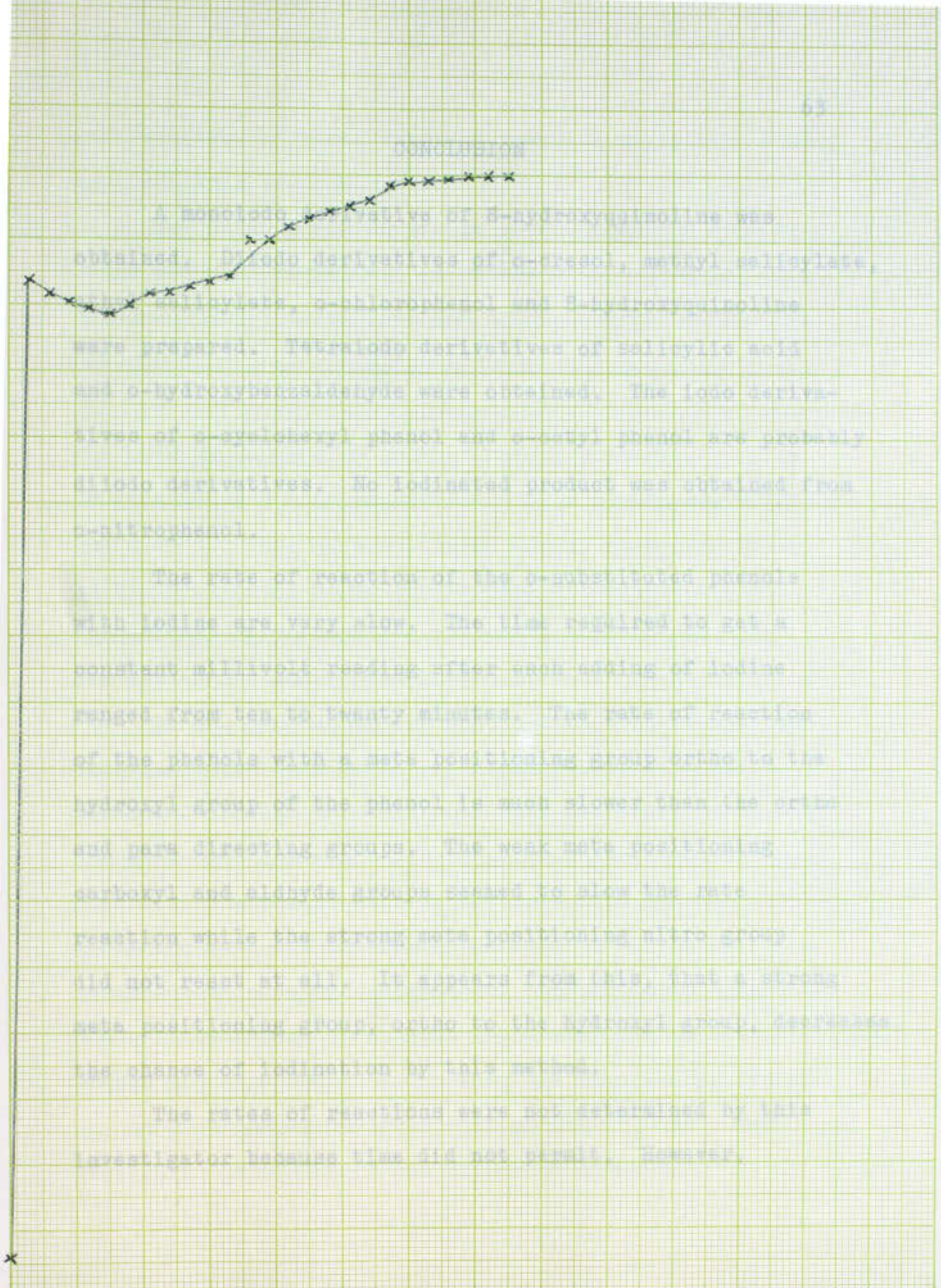
One gram of o-nitrophenol was dissolved in as little sodium hydroxide as possible, 200 ml. of 7.1% ammonia solution added and then 0.5502N iodine in potassium iodide solution was added with stirring 3 ml. at a time until the color of iodine persisted. The potential in millivolts was read after the addition of each three ml. of iodine solution.

After completion of the reaction, the excess iodine was reduced to iodide with sodium bisulfite and then the solution was acidified with dilute sulfuric acid. No product was obtained. Several attempts were made to obtain an iodinated product from o-nitrophenol but all failed.

TABLE X

POTENTIAL DATA FOR THE REACTION OF IODINE WITH O-NITROPHENOL IN 7.1% AMMONIA SOLUTION

Ml. 0.5502N Iodine	Potential in Millivolts
0	-135
3	234
6	229
9	226
12	224
15	223
18	225
21	229
24	230
27	232
30	234
33	236
36	250
39	250
42	255
45	258
48	261
51	263
54	266
57	268
60	270
63	270
66	271
69	272
72	272
75	272



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CONCLUSION

A monoiodo derivative of 8-hydroxyquinoline was obtained. Diiodo derivatives of o-cresol, methyl salicylate, ethyl salicylate, o-chlorophenol and 8-hydroxyquinoline were prepared. Tetraiodo derivatives of salicylic acid and o-hydroxybenzaldehyde were obtained. The iodo derivatives of o-cyclohexyl phenol and o-octyl phenol are probably diiodo derivatives. No iodinated product was obtained from o-nitrophenol.

The rate of reaction of the o-substituted phenols with iodine are very slow. The time required to get a constant millivolt reading after each adding of iodine ranged from ten to twenty minutes. The rate of reaction of the phenols with a meta positioning group ortho to the hydroxyl group of the phenol is much slower than the ortho and para directing groups. The weak meta positioning carboxyl and aldhyde groups seemed to slow the rate reaction while the strong meta positioning nitro group did not react at all. It appears from this, that a strong meta positioning group, ortho to the hydroxyl group, decreases the chance of iodination by this method.

The rates of reactions were not determined by this investigator because time did not permit. However,

determination of these rates of reaction would make a very good research project.

The exact position of the entering iodine atom or atoms was not determined in every case. However, when diiodo-o-methyl salicylate and diiodo-o-ethyl salicylate were reacted with potassium hydroxide to determine their saponification equivalents, the acid products were identical. The acid decomposed at 228°C. From information obtained in literature 3,5-diiodosalicylic acid decomposes at about 230°C.(16). From this one could assume that positioning of the two iodine atoms in diiodomethyl salicylate and diiodoethyl salicylate are in the 3,5 positions with respect to the ester groupings.

It was assumed at the start of this investigation that salicylic acid and o-hydroxybenzaldehyde would produce diiodo substituted products. However, tetraiodo products were obtained. The reaction with halogens occurs with especial ease in the case of a hydrogen atoms which are adjacent to certain groups, above all the carbonyl and carboxyl groups(32). Hexane, even with only 50% of the amount of bromine neccessary for monosubstitution, yields not only monobromo hexane, but also a considerable amount of higher brominated compounds(33). The above statements help clarify the situation somewhat.

The products from the iodination of both o-cyclohexyl phenol and o-octyl phenol were tarry masses and could not be obtained in crystalline form. These two products are probably polymers of some type. In the presence of alkali and iodine, an o-alkyl or aryl phenol undergoes iodination and subsequent polymerization[36]. From this one could assume that the products are true iodinated products and the iodine is not absorbed in the molecule itself.

Examination of potential curves taken during the iodination of the o-substituted phenols shows that the curves have certain differences. This may be due to the fact that the compounds are only similar in that they are all o-substituted phenols and are not chemically similar. Some of the curves break sharply upward at certain points on the abscissa and give indications to the amount of iodine that has entered the ring. The potential curves, of those compounds which substituted four atoms iodine do not give sufficient information to predict that four atoms of iodine had entered the ring. In the case of the potential curve for the reaction of o-nitrophenol with iodine, the result is in close agreement with the potential curve(Fig. 2) that Gill obtained when iodination did not take place. The nitrogen triiodide which usually formed right at the first

of each reaction and then disappeared may account for the first downward break in some of the curves. From this it might be assumed that nitrogen triiodide might act as an initial catalyst or carrier for iodinations in ammonia solutions.

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